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EXAMINER	
NOAKES, SUZANNE MARIE	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/817,058	BAKER ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The amendments to claims filed 17 March 2007, canceling all previous claims and adding new claims 59-76 are acknowledged. The petition under 37 C.F.R. 1.47 has been decided by the Office of petitions. The declaration filed under 37 C.F.R. 1.131 is acknowledged and under consideration. Claims 59-76 are pending and subject to examination on the merits.

Withdrawal of Objections/Rejections

2. Any rejection not explicitly recited below is hereby withdrawn.

New Rejections – Necessitated by Amendments

Claim Objections

3. Claims 59-67 are objected to because of the following informalities: The tenses and phrasing of the instant claims are grammatically inconsistent. It is noted that the present participle/gerund "administering" is inconsistent with the past tense of 'a patient subjected to an ischemic event' (past tense). Thus amending said claims to be grammatically consistent is suggested.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 60 and 63-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 60 and 63-65 state that the method is drawn to administering an amount of erythropoietin (EPO) for a time period of about 15 minutes at a time prior to the onset of ischemic event, wherein said time period prior is 1-35 minutes (claims 60 and 64-65) or 1-20 minutes prior (claim 63). However, in the time period of 1-35 minutes prior to an event, if the administration is 15 minutes long, then at anytime from 1-14 minutes, the administration will no longer be "prior to an ischemic event" and will in fact proceed into the commencement phase of the ischemic event. The claims, on the contrary, make clear that the administration must occur prior to the ischemic event. Analogously, for the 1-20 minute time period prior to an ischemic event, only 15-20 minutes prior to the event will be a time sufficient to accommodate a 15 minute dosage period. However, these time frames are not noted anywhere in the specification.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 59-65 and 67-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the effects of myocardial ischemia in a patient, comprising the step of: administering erythropoietin for an about 15 minute period to a patient prior to the patient being subjected to an ischemic event in an amount effective to activate PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channels, wherein the activation reduces the effects of myocardial ischemia, does not reasonably provide enablement for methods of treating myocardial ischemia by activating any other potassium channels or protein kinases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to methods for reducing the effects of myocardial ischemia by administering to a patient in need thereof an effective amount of EPO for a 15 minute time period so as to activate either a protein kinase or potassium channel, which, according to the specification, EPO activation of protein kinases or potassium channesls provides a cardioprotective effect (p. 4, first full paragraph). However, other than PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channel, the specification fails to provide guidance regarding other protein kinases and potassium channels – if any – that will be activated by EPO and provide a cardioprotective effect. Thus, other than an effective amount of EPO to activate PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channels, one skilled in the art would not be apprised of what other amounts of EPO are

considered to be effective amounts to activate any and all protein kinases or potassium channels in order practice the full scope of the claimed invention. Thus, considerable undue experimentation is required by a skilled artisan to determine which kinases and potassium chancels other than PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channels – if any – are involved in ischemia and activated by EPO and the effective amounts of EPO that are required to activate these protein kinases or potassium channels.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, there is considerable doubt that all kinases and potassium channels will be involved in ischemia and activated by EPO. Furthermore, there is reasonable doubt that all potassium channels are involved in ischemia and are effected by EPO (see Shi et al. Basic Res. Cardiol., 2004, 99:1-10 – cited on IDS). Both the specification and prior and post-filing art suggest that only a select few kinases are involved in the ischemic process. The specification provides guidance as to only PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channels that are effected in ischemia (see p. 1, last paragraph, to p. 2, first two paragraphs). Furthermore, Shi et al. note that PKC-epsilon, p38 MAPK, p42/44 MAPK, JNK – protein kinases or ATP-sensitive K+ channels are the only known kinases and potassium channels that are activated in response to EPO. Thus, the direction and guidance in both the prior art, the specification, and the working examples all suggest that the scope of the claims exceeds that which is being claimed, e.g. all protein kinases and potassium channel activation will be effected by EPO and administration of said EPO will reduce the effects of myocardial ischemia through the activation of these channels. Since this is not the case, one skilled in the art would necessarily have to practice a considerable amount of undue experimentation to ascertain if any others are involved in the myocardial ischemic process, whether or not these are affected/activated by EPO, and to determine an "effective amount" of EPO that will result in such activation.

Thus, when the relevant Wands factors are considered in their entirety, the scope of the claims exceed that which they are enabled.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.

9. Claims 59-76 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Applicants' reply and 37 C.F.R. 1.131 declaration filed 15 March 2007 (and earlier Declarations) casts considerable doubt and ambiguity as to the inventive entities listed on the instant filed US patent application. On 02 April 2004, a sworn Oath and Declaration was filed claiming benefit of US provisional application 60/460,684 and naming both John Baker and Yang Shi as inventors and swearing that all statements made within said Oath are believed true with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom. Both John Baker and Yang Shi signed and executed the Oath on 02 April 2004. The following is noted regarding any signed Oath or Declaration filed under 37 CFR 1.63.

> MPEP 2137.01 (I): ***The party or parties executing an oath or declaration under 37 CFR 1.63 are presumed to be the inventors***. *Driscoll v. Cebalo*, 5 USPQ2d 1477, 1481 (Bd. Pat. Inter. 1982); *In re DeBaun*, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982"

It is further noted that the inventors of said signed oath must actually have contributed to the *conception* of the invention.

> See MPEP 2137.01 (II): "***The definition for inventorship can be simply stated: "The threshold question in determining inventorship is who conceived the invention. Unless a person contributes to the conception of the invention, he is not an inventor."*** See MPEP § 2138.04 - § 2138.05 for a discussion of what evidence is required to establish conception or reduction to practice.

Thus, each and every person named on the US patent application must have contributed to the conception of the invention.

> See MPEP 2137.01 (V): "***Each joint inventor must generally contribute to the conception of the invention.*** A coinventor need not make a contribution to every claim of a patent. A contribution to one claim is enough."

However, the 37 C.F.R. 1.131 Declaration filed 15 March 2007 clearly suggests the contrary and that all listed inventors did not contribute to conception. Even though Applicants were granted the right to waive the requirement that Yang Shi must sign the 1.131 Declaration, the Declaration necessarily is presumed to be factual and accurate and those signing it have made sworn statements as noted on p. 7 of said Declaration under Section 1001 of Title 18 of the United States Code that the statements and facts made therein are true.

As noted, the information supplied in the Declaration, however, suggests that Yang Shi, a named inventor, had nothing to do with the conception of the invention. The following are limited excerpts of the 1.131 Declaration submitted 15 March 2007

highlighting areas indicating that the listed inventor, Yang Shi, is questionable to the aspect of conception and thus inventorship.

I, John E. Baker, Ph.D., being an inventor and applicant in the above-identified patent application, declare and say as follows:

1. ***That on a date prior to December 29, 2000, I, Dr. John E. Baker, conceived of a method*** of increasing resistance of the heart to injury from ischemia utilizing erythropoietin (EPO). This is evidenced, at least in part, by the following exhibits:

(a) Exhibit A, which is a copy of a page of a research notebook dated May 29 1998, **with my observations** and notes of a presentation on the identity of known triggers of the late phase of ischemic preconditioning. The notebook page includes **my notation** of the use of erythropoietin (EPO) to confer late preconditioning against injury from ischemia, where there is a time delay between administering erythropoietin and subjecting the heart to ischemia/reperfusion.

(b) Exhibit B, **which is a copy of my notations** on the backside of the confirmation of hotel reservation (dated March 30, 2000) prior to the International Symposium (The Developing Heart) in Prague, Czech Republic on May 18-20, 2000. The notations were made on a date between March 30, 2000 (receipt of hotel confirmation) and May 11, 2000 (date of travel to the Prague meeting).

(c) Exhibit C, entitled "Rationale", is a **copy of a proposed slide that I prepared** between March 30 to May 11, 2000, **for my talk** at the Prague meeting (May 18-20, 2000), but was not included in the presentation.

d) Exhibit D is **a copy of a slide that I prepared** between March 30 to May 11, 2000, for my talk at the Prague meeting

e) Exhibit E is **a copy of a document that I prepared** on or about August 10, 2000, which records the experimental conditions to conduct an animal study to demonstrate immediate cardioprotection by administering erythropoietin when

given prior to an ischemic event, during an ischemic event, and after an ischemic event.

However, now turning to point 2., on page 3 of the Declaration the following highlighted areas are of particular concern.

2. That from the date of conception prior to December 29, 2000 to April 4, 2003, **I, Dr. John E. Baker, in part with Dr. Yang Shi, diligently pursued this invention up to the April 4, 2003** date of filing the provisional application S/N 60/460,684 to the above-identified patent application in the U.S. Patent and Trademark Office.

(a) **I conducted initial research studies** from May 2000 to December 2001 to determine the mechanisms stimulated by chronic hypoxia that result in increased resistance to ischemia.

(i) These studies were conducted in order to develop a model to use in testing and validating the effect of administering erythropoietin to cause the same effect as chronic hypoxia (i.e., increased protection of the heart against injury from ischemia) but in the absence of chronic hypoxia.

(ii) As I had set forth in Exhibits C and D, my rationale was that administering erythropoietin prior to an ischemic event (and in the absence of chronic hypoxia) would result in an increased level of erythropoietin to activate protein kinases and nitric oxide synthase which will result in resistance to ischemia.

However, there is nowhere mentioned anywhere, of what part Yang Shi played in the conception of the invention. As noted above, any listed inventor of a US Patent Application *must* have contributed to the conception of the invention. Inventor John Baker further states on p. 3 of the Declaration:

Part (b) on p. 3 states that: "**I published the results of initial research studies**" for Exhibits F-H.

Part (c) on p. 4 states that: "Based on the result of the studies, I developed a model that involved monitoring.....".

In part (d) of page 4, it is stated that on **September 11, 2001 I submitted a research proposal entitled Erythropoietin, Nitric Oxide Synthase and Resistance to Myocardial Ischemia**"

In part (e) of page 4: "On or about December 19, 2001, **Dr. Yang Shi and I (Dr. John E. Baker)** ***directed and supervised*** a research study on administering EPO to demonstrate and confirm the effect of administering EPO....."

In part (f) of p. 5 it is stated: "On or about May 9, 2002, **Dr. Yang Shi and I (Dr. John E. Baker) submitted** ***a Discovery Record and Report*** entitled "Cardioprotection by Erythropoietin"

Thus, once again, there is no evidence that Yang Shi contributed to any part of the conception of the invention.

Likewise, the sworn 37 1.131 C.F.R. Declaration of 10 July 2006, also indicates that Dr. John E. Baker conceived of the method and that Yang Shi merely in part with Dr. Baker diligently pursued the invention (see p. 1, points 1 and 2). Dr. Baker was the only signing inventor in this instance.

However, adding to the confusion is the sworn Declaration filed under 37 C.F.R. 1.131 filed 05 August 2005, signed by both John Baker *and* Yang Shi. It is stated that Dr. John Baker, at that point in time, was only "involved in the conception" (and not that

he was the sole conceiver of the invention as stated in the later Declarations); and that a study of formulations of EPO was conducted under **our** supervision.

As further confusion, is that while Yang Shi was willing to sign the first Declaration of 05 August 2005, she was unwilling to sign the subsequent declarations as noted by Applicants in her email correspondence from 15 June 2006 (see Exhibit 3 of Petition filed under 1.47 on 15 March 2007 and 10 July 2006).

These contradictory statements provide reason to question the inventorship of the claimed invention, particularly as to whether or not Yang Shi is actually an inventor of the invention as claimed. Because of these ambiguities regarding inventorship and conception, it is incumbent on applicants to provide a satisfactory showing that would lead to a reasonable conclusion that applicants (John Baker *and* Yang Shi) are the inventors of the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 59-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brines et al. (US 6,531,121) as evidenced by Parsa et al. (J. Clin. Med. October 2003, 112: 999-1007), Shi et al. (Basic Res. Cariol., 2004, 99:1-10 – cited on IDS) and Cavillo

et al. (PNAS, epub March 2003, 100(8):4802-06 – cited previously on PTO-892 from 11/03/2004) in view of Rubsamen (US 6,012,450).

The claims are drawn to methods of reducing the effects of myocardial ischemia by administering to a patient in need thereof an effective amount of erythropoietin (EPO) for a time period of about 15 minutes (continuous) so as to activate production of a protein kinase; with various limitations requiring blood serum levels achieved within various time frames after the administration has occurred; and wherein administration of EPO occurs at different time frames including prior to ischemic (claims 59-67), after an ischemic event (claims 68-70) or wherein the EPO is administered at commencement of reperfusion (claims 71-73) or during reperfusion (claims 74-76).

Brines' et al. teach methods of treating or preventing ischemia in patients suffering from various ischemic events wherein administration is given prior to an ischemic event, at the start of said event and after the on-set of an ischemic event (e.g. myocardial or neural ischemia (see Examples 3 and 5)), and also to preserve and treat organs used in transplants in order to prevent or treat an ischemic event in an organ transplant recipient patient wherein the EPO is perfused throughout the organ. Both methods achieve these results through the use and/or administration of erythropoietin (EPO) in specific doses. It is further taught that the dosing and frequency is performed by one skilled in the art so as to achieve the desired effects (e.g. reduction in ischemia and induction of EPO receptor) [see column 4, lines 26-37).

Brines et al. teach a thorough background regarding EPO and the rational and reasons for the success of their invention. For many years, the only clear physiological

role of erythropoietin (EPO) was thought to be its control of the production of red blood cells. However, several lines of evidence suggested that EPO, a member of the cytokine superfamily, performed other important physiologic functions which were mediated through interaction with the erythropoietin receptor (EPO-R). These actions included mitogenesis, modulation of calcium influx into smooth muscle cells and neural cells, and effects on intermediary metabolism. It was believed that EPO would provide compensatory responses that would serve to improve hypoxic cellular microenvironments. (A hypoxic environment is defined as an environment where oxygen is limited or at a lower concentration than normal. A hypoxic environment is induced in tissues or organs whenever an ischemic event takes place in said tissue or organs.)

Thus, Brines et al. teach that their invention is the identification of tissues and organs where EPO can migrate across tissue barriers that were previously thought impenetrable to EPO, and therefore identifying new methods of treating patients and/or organs prone to ischemic damage by using EPO. The following is a summary of their inventions: EPO can be successfully administered or perfused in any organ and/or tissue which has erythropoietin responsive cells (column 11, lines 33-50) such as retinas, lungs, kidneys, neurons or heart (column 4, lines 13-25).

Thus, Brines et al. have identified several tissues and/or organs which previously were thought not to be responsive to EPO, such as the brain, retina's of the eyes and the heart. As way of a very specific example (see Example 3, and Figure 2), Brines et al. teach a method of protecting the myocardium from ischemic injury by administering

5000 U/kg erythropoietin (EPO) 24 hours prior and again immediately before an induced ischemic event to the heart. The results were measured by measuring the pressure of the left ventricular pressure of the heart (see Figure 2). The results showed significantly less damage to the heart which was protected/treated with EPO as compared to the heart which was treated/protected with saline as the control.

Brines' et al. teach the following concentrations of EPO to be administered to a subject and the resulting blood/serum concentration level achieved when said concentrations of EPO are administered, and finally, the time in which to expect the EPO blood/serum concentration to be achieved.

> In a preferred embodiment, an erythropoietin may be administered systemically at a dosage between 100 nanograms to about 50 micrograms per kg body weight, preferably about 20 micrograms to about 50 micrograms per kg-body weight. In the instance where an erythropoietic erythropoietin is used, the range may preferably be about 20 micrograms to about 50 micrograms per kg body weight. This effective dose should be sufficient to achieve serum levels of erythropoietin from about 10 picograms to about 1000 nanograms per ml of serum after erythropoietin administration. Such serum levels may be achieved at about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours post-administration (column 12, lines 19-39).
>
> For other routes of administration, such as by use of a perfusate, injection into an organ, or other local administration, a pharmaceutical composition will be provided which results in similar levels of an erythropoietin as described above. A level of about 10 pg/ml to about 1000 ng/ml is desired (column 12, lines 56-61).

In order to further understand the inventions taught by Brines' et al., as well as the limitations of the claims in the instant application, it is necessary to understand that one unit (U) of EPO, with a MW of approximately 34,000 Da, is equivalent to 10 ng of protein and thus one mg of protein is equal to 100,000 U (column 11, lines 14-16). Thus

based upon the fact that 1 U EPO = 10 ng (and 10^{-5} mg); then the Brines' et al. preferred embodiment for systemically (parenterally) administering a dosage between 100 nanograms to about 50 micrograms per kg body weight, is equal to 10-5000 U/kg. Likewise, Brines' et al. preferable dosage is from about 20-50 μg/kg which is equal to 2000-5000 U/kg (Both of these doses encompass the dosage range in instant claim 66).

Also, central to both Brines' et al. invention, and also the claim limitation of the instant application, is the blood/serum concentration achieved after administration of EPO has occurred. Thus, also based on the above conversion numbers (1 U EPO = 10 ng (and/or 10^{-5} mg), Brines' et al. teach that the achieved EPO serum/blood concentration will be in the range of 10 picograms to 1000 nanograms, which is equal to .001-10 u/ml (based upon administration of 2000-5000 U/kg EPO). This concentration as taught by Brines et al. specifically spans the range of instant claims 62-65, 69, 72 and 75. It should also be noted, that Brines et al. also teach that in terms of other local administration routes, such as local administration or perfusing an organ with the same amount of EPO, that the same EPO blood/serum concentration is achieved.

Brines' et al. teach the ranges of EPO to be administered and the blood concentration achieved after administration that will prevent or treat an ischemic event, specifically in the heart. Brines' et al. teach a greater range (10-5000 versus 50-5000 U/kg) as well as a greater range expected for the EPO blood/serum concentration (.001-10 versus 0.5-10 U/ml) which can be used to activate production of protein kinase. It is noted that while Brines et al. do not specifically state that EPO activated protein kinase

production or the signaling cascade involved in protein kinase production, this effect of EPO is an inherent property of the compound. Administration of EPO will always and necessarily produce protein kinases given the effective amount that is being administered. This is evidenced by post-filing art of Parsa et al. (J. Clin. Invest., October 2003, 112: 999-1007 – cited on IDS from 07-07-2004) that state stimulation EPO and EPO-Receptor (e.g. by administration) activates protein kinase cascades, which are in turn dependent upon potassium channel activation (see Shi et al. Basic Res. Cariol., 2004, 99:1-10 – cited on IDS). Parsa et al. cite three other references supporting this conclusion. (see p. 1005, 2nd column, 2nd full paragraph). Thus, this is an inherent function of EPO to activate protein kinase cascades and potassium channels.

Finally, Brines et al. also teach that administration of EPO can be performed by various modes that will slowly and continuously administer EPO such as transdermal patches or osmotic pump (see column 15 and lines 40-43), in controlled release systems well known to those in the art (see column 15, lines 63-67) or by suppositories, which will release EPO slowly and continuously over a period of time (see column 15, lines 13-15). Thus Brines et al. teach methods to deliver EPO to a mammal in a slow and continuous manner by methods that are very well known to those in the art. (This limitation of continuous administration for 1-35 minutes is addressed in claim 3). Administration is specifically taught by way of Example as prior to the on-set of ischemia, at the on-set of ischemia and after the on-set of ischemia (see Example 3).

Brines et al., however, do not explicitly teach the exact time range that spans the length of the time of administration of EPO or the exact moment of administration, e.g. continuous administration for an about 15 minute period before, at the commencement and/or during reperfusion or the exact time in which the desired EPO blood levels are achieved.

Rubsamen teaches a method of treating human patients by using an intrapulmonary device which administers EPO to a patient in need there of for a continuous time period of 15 minutes (see column 8, lines 11-36 and column 9, lines 32-40). The method is advantageous over other deliver methods as it delivers EPO to the lungs which is then absorbed into the blood stream quickly and efficiently (see column 3, liens 1-9).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the treatment in a slow continuous treatment regiment of Brines et al., wherein the teachings are to administer 10-5000 U/Kg of EPO to a patient in need thereof and to administer said amount of EPO for a continual time period of 15 minutes as taught by Rubsamen in order to effectively and quickly administer said EPO to the blood stream in an efficient and quick manner so as to provide cardio protective effect to said patient suffering from a mycarodial ischemic event.

One would be motivated to combine the two teachings because Brines et al. teach the necessary dosage and concentrations of EPO administration to achieve protection from myocardial ischemia and Rubsamen teaches the benefits of

administering EPO in a 15 minute time period via pulmonary inhalation, which provides the advantage of quick and efficient deliver of EPO to the blood stream.

It is noted that the cardio protective effect that lessens the effects of myocardial ischemia is in part a result of EPO's effect on the protein kinase cascades and potassium channels as noted above by Parsa et al. and Shi et al. The blood serum level which is achieved would necessarily be the same in Brines et al. and in the instant invention (see claims 62-65, 69, 72 and 75) because an effective amount is defined in the instant specification (and in claim 66) as 50-5000 U/Kg. It is specifically noted that the instant specification states on p. 4, lines 9-17:

> While not meant to limit the invention, it is believed that one way that erythropoietin can reduce the injury caused by ischemia and provide a substantially immediate cardioprotective effect is by activating potassium channels and protein kinases. Accordingly, the invention also provides a method of activating a cardioprotective signaling pathway, for example, to activate a protein kinase (e.g., MAP kinase) or a potassium channel (e.g., KATP) to provide a cardioprotective effect. Preferably, a composition containing an effective amount of EPO to result in a blood level of about 0.5-10.0 U/ml EPO substantially immediately after administration, preferably within about 1-20 minutes, with a preferred dose amount being about 50-5,000 U/kg of EPO.

Also as noted above, Brines et al. teach this range/amount to administer to a patient in need thereof.

The claimed time of administration of said EPO e.g. prior to, at the on-set, during or commencement of reperfusion will also necessarily achieve the same results (e.g. activation of a protein kinase, achieving a blood serum concentration of EPO and/or within a desired time of 1-35 or 1-20 minutes) because the same amount of EPO is being administered and said amount is the crucial aspect which provides the protection

of the tissues (e.g. the heart) and which activates the protein kinase cascades and hence the production of various protein kinases. While Brines et al. does not specifically teach administration at commencement and during reperfusion, one of skill in the art would expect to achieve the same results as administration either before or after an ischemic event has occurred. It is noted that reperfusion is the time period in between that which is taught by Brines et al. and thus administration during this time frame would necessarily be expected to have the same results of prior or post-administration results. It is noted that administration of EPO at the start of reperfusion (which if one administers EPO for 15 minutes at the start of reperfusion, one necessarily is also administering *during* reperfusion) does in fact give the same results as administration prior to an ischemic event (see Cavillo et al., which is a Brines patent post-filing reference, who teach there is no difference between the myocardial protection afforded by pre-treatment and treatment during reperfusion, see p. 4803, 2nd column, 1st two paragraphs and p. 4804, *In vivo* Experiments). Thus, there would be a great expectation of success that this "effective amount" e.g. 10-5000 U/kG as taught by Brines et al. would achieve the same blood serum levels of 0.5-10 U/ml as claimed when administered for a 15 minute time period as taught by Rubsamen, regardless of when administration occurs.

Therefore it would have been *prima facie* obvious to combine Brines et al. and administering EPO in an amount of about 10-5000 U/Kg for an extended period, which will necessarily activate protein kinase cascades and thus the activation of protein kinases within 1-35 minutes and achieve blood serum levels of 0.5-10 U/ml, wherein

said administration is for about a 15 minute time period either prior to, after the on-set of an ischemic event or at commencement or during reperfusion, in order to treat effects from myocardial ischemia by activating various protein kinasases and potassium channels.

12. Claims 59-76 are rejected under 35 U.S.C. 103(a) as being anticipated by Stamler (US 2004/0009908) as evidenced by Parsa et al. as detailed above in view of Rubsamen (US 6,012,450) as taught above.

Stamler teaches methods of reducing myocardial oxidative or nitrosative stress caused by either hypoxia or ischemia in patients by administration of erythropoietin (EPO) at a concentration less than 5000 U/kg (see claims 1-73, specifically claims 1-3 and 9-11, and p. 2, paragraph [0009]). The instant claims recite that the EPO is administered in an effective amount to stimulate the production of a protein kinase prior to, at the on-set, of an ischemic event, at commencement of reperfusion or during reperfusion. Some of the instant claims recite administering EPO for a 15 minute time period prior to an ischemic event in an amount effective to achieve a blood concentration of 0.5-10 U/ml (claim 62-65) within about 1-35 minutes or 1-20 minutes prior to the ischemic event; or in amounts of 50-5000 U/kg (claim 66). While Stamler concentrates on not increasing the hematocrit levels, rather than the time in which a blood serum level will be achieved post administration or rather that administration of EPO will activate a protein kinase, the exact same result is achieved. As noted above, Parsa et al. descibes and provides evidence that it is known in the art that stimulation of EPO (e.g. administration of EPO or natural production of EPO) and the stimulation of its

receptor necessarily results in the activation of protein kinase cascades; in other words, several protein kinases will be activated because of the administration of EPO. Thus, administration of the same compound, EPO, in the same concentration, to the same patients suffering from the same myocardial ischemia will necessarily activate a protein kinase. In this respect there is no difference between the teachings of Stamler and that which is being claimed because the means to achieve that which is being claimed is identical to Stamler. Furthermore, Stamler teaches administration of EPO to treat myocardial ischemia wherein said EPO is administered prior to or during a myocardial ischemic event, at commencement of reperfusion and/or during reperfusion (see claims 22-24). Finally, Stamler teaches that the dose can be a single dose or a continuous dose of EPO to someone suffering myocardial infarction (see claims 39-44).

Stamler, however, does not teach how long the time period is for a continuous dose of EPO or that it is about a 15 minute time period.

The teachings of Rubsamen are detailed in the previous Section above.

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Stamler, who teaches administering 50-5000 u/Kg of EPO to treat myocardial ischemia either prior to, at the on-set or subsequent to said ischemic event or subsequent to reperfusion and to administer the EPO over a long continuous time period of about 15 minutes as taught by Rubsamen in order to quickly and efficiently get said EPO into the blood stream.

It is specifically noted that the instant specification states on p. 4, lines 9-17:

> While not meant to limit the invention, it is believed that one way that erythropoietin can reduce the injury caused by ischemia and provide a

> substantially immediate cardioprotective effect is by activating potassium channels and protein kinases. Accordingly, the invention also provides a method of activating a cardioprotective signaling pathway, for example, to activate a protein kinase (e.g., MAP kinase) or a potassium channel (e.g., KATP) to provide a cardioprotective effect. Preferably, a composition containing an effective amount of EPO to result in a blood level of about 0.5-10.0 U/ml EPO substantially immediately after administration, preferably within about 1-20 minutes, with a preferred dose amount being about 50-5,000 U/kg of EPO.

Thus, this suggests, administration of EPO at the preferred dose amount of about 50-5,000 U/kg of EPO, will necessarily achieve the desired results in the time period stated and also activate said potassium and protein kinase channels. One of ordinary skill in the art would have a considerable expectation of success that if they administered the exact same amount of EPO as taught in Stamler, which is the exact same "preferred dose amount being about 50-5000 U/Kg", for an extended time period such as continuous 15 minutes of administration such as is taught by Rubsamen, then one would necessarily achieve activation of a protein kinase, the requisite blood serum levels and with the stipulated time frame as stated in the claims.

One of skill in the art would be motivated to combine the two teachings because Rubsamen teach that a 15 minute administration of EPO via pulmonary inhalation results in quick and efficient deliver of EPO and thus one would be motivated to use this delivery system with the administration protocol of Stamler in order to administer 50-5000 U/kG of EPO to treat myocardial ischemia.

Response to Arguments

13. Applicant's arguments filed 10 July 2006 have been fully considered but they are not persuasive for the reasons stated below.

14. The Declaration filed on 10 July 2006 under 37 CFR 1.131 has been considered but is ineffective to overcome Brines et al. (US 6,531,121 – Effective Filing Date of 29 December 2000).

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Brines et al. reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). Applicants have submitted several Exhibits (A-M) in order to establish conception and due diligence prior to the filing date of the Brines et al. patent. However, noted above in the 35 U.S.C. 102(f) rejection, the actual conception of the invention as it is not apparent how both inventors conceived of the instant invention. Dr Shi's contribution to the conception appears well after the effective filing date of Brines et al. and establishes that both inventors had involvement in the conception of the instant invention only from the date of 19 December 2001 onwards, which is the first date of result of the first test of the proposed research (Exhibit J – dated 09 May 2002). Thus, Applicants have failed to establish a case of conception prior to the Brines et al. date and thus the declaration is insufficient to overcome the prior art of record.

15. The evidence submitted is insufficient to establish diligence from a date prior to the date of reduction to practice of the Brines et al. reference to either a constructive reduction to practice or an actual reduction to practice. Applicants have submitted Exhibits A-M, to establish that Dr. Baker and Dr. Shi diligently pursued the invention from the date of conception, 29 May 1998, up to the date of filing on 04 April 2003.

However, it is particularly noted that from the time of the first purported conception there is a significant gap between *29 May 1998* and the copies of notations and slides prepared as shown Exhibits B-D which are purported to have been prepared *between 30 March 2000 and 18-20 May 2000*; which is a gap of nearly two years. Applicants have done nothing to demonstrate that anything was done in between 29 May 1998 and 30 March 2000. It is further noted, Applicants show in Exhibit E experimental conditions to conduct an animal study to demonstrate immediate cardio protection by administering EPO prior to an ischemic event and this was prepared 10 August 2000. However, this begs the question then, if the proposed animal study protocols were prepared at this time, why did it take until *19 December 2001* to actually perform the first experiment which is the date recorded on Exhibit J (dated 09 May 2002), which is a gap of nearly 1 ½ years? What was done in the time in between to pursue the claimed invention? Applicants have submitted several journal articles, such Exhibit F (a study conducted between March 1998 and 2000 and published in 2000), Exhibit G (a study conducted between January 2000 to December 2000, published in 2001) and Exhibit H (a study conducted between December 2000 to January 2002 and published in 2002); however, notably, ***none*** of these journal articles ever test, discuss,

or detail anything linking the use of EPO and the treatment of an ischemic event. Thus, these articles seem irrelevant to establish diligence of the ***claimed invention***.

Applicants also have submitted additional journal articles, Exhibits K-L, published between December 2001 and April 2003 to establish further diligence up to the filing of the Provisional Application 60/460,684. However, again it is specifically noted that *nothing* in these journal articles ever mentions, describes, tests, uses EPO in any way or establishes a correlation between reduction in ischemia and administration of EPO, which ***is*** what the claimed invention is directed to. It is not until Exhibit M, which is a publication in 2004 that any type of link or actual results are described which establish a nexus between the *claimed invention* and any of the journal articles submitted by Applicants as evidence/Exhibits. Exhibit M clearly establishes what the search and discovery report described in Exhibit J, *dated 19 December 2001*, teaches (however, notably, again, nearly two years have lapsed between the date of Exhibit J, and the time of filing of the provisional Application, and an even great time for the publication of Exhibit M). Applicants did file the provisional Application, as noted above, 04 April 2003. However, they have failed to establish (and to realize) diligence necessarily has to be established up to the time of filing the instant Non-Provisional Application.

Applicants again are reminded, MPEP 715.07(a) clearly states: "Where conception occurs prior to the date of the reference, but reduction to practice is afterward, it is not enough merely to allege that applicant or patent owner had been diligent. *Ex parte Hunter*, 1889 C.D. 218, 49 O.G. 733 (Comm'r Pat. 1889). Rather, applicant must show evidence of facts establishing diligence." In the instant case,

Applicants have not shown any evidence of diligence which would cover the time span between the first alleged conception of Exhibit A (29 May 1998) to the next report of conception of between March 30 and May 18-20 2000 (Exhibits B-D/E) to the date and time of the first test of the conceived idea (19 December 2001) to the time of filing the Provisional Application 04 April 2003 and the instant Non-Provisional filed 02 April 2004. There are too many gaps in between these events which Applicants are attempting to fill with superfluous journal articles which have nothing to do with what is actually being *claimed,* e.g. the use of EPO prior to an ischemic event to treat ischemia. Thus, there is a lack of reasonable due diligence and the affidavit is ineffective to overcome the art of record.

Conclusion

16. The declaration of record filed under 37 C.F.R. 1.131(b) 15 March 2007 to overcome the previous rejections, and now the instant rejections, in view of Brines et al. or Stamler, said declaration is ineffective to overcome said rejections for the reasons noted above. It should be noted that although Stamler is no longer a pending Application, the declaration still fails to overcome the 35 U.S.C. 102(a) date of PG-Pub.

17. The rejections of record cited in the Final Office action from 10 April 2006 are maintained as the Declaration filed under 37 C.F.R. 1.131 is ineffective to overcome the art of record for the reasons cited above.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
12 September 2007

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656